NERVOUS AND OTHER FORMS OF PROTO-PLASMIC TRANSMISSION.   II

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TRANSMISSION-PHENOMENA of a closely similar kind have in fact long been known in certain definitely constituted inorganic systems which, superficially considered, appear to have little in common with living tissues, namely, combinations of metals with electrolyte solutions.   Many metals in contact with aqueous solutions of salts and other electrolytes readily undergo local chemical change which is accompanied and conditioned by the flow of electricity between the reacting regions of the metallic surface.   The rusting of iron in water or salt-solution is a familiar example of this type of process. Such processes depend ultimately upon certain widely general conditions which have their seat at the surface of contact between metal and solution, and which are common, broadly speaking, to all surfaces of contact between chemically dissimilar liquids and solids.   These conditions are present at the boundary between the living cell and its medium, as well as at the boundary between an oil droplet or colloidal particle and its suspension-fluid, or between a metallic surface and the adjoining solution, and their essential nature may be thus briefly defined.   On account of the different relations which the ions present in either phase, or formed by reaction at the boundary, have to the two adjoining phases, there is usually a difference of electrical potential across the boundary.   Potentials of this kind (interfacial potentials) indicate a tendency to spontaneous chemical change in the substances at the boundary, and if such changes occur they may give rise under certain conditions to electric currents which secondarily may form the condition of further chemical change either in the same or in adjoining systems.   These conditions are exemplified in a typical manner in the phenomena of electrolysis, familiar wherever an electric current passes between a metal and a solution.   A battery in which chemical and electrical change proceeds spontaneously (when the circuit is closed) will cause chemical decompositions or other reactions (including syntheses under certain conditions) in an otherwise inactive solution into which its electrodes dip.   These electrically induced reactions take place at the surface of the electrodes, within the thin layer of material,

presumably one molecule in thickness, where electricity passes between the two phases; *i. e.,* they are distinctively *surface phenomena;* and strict numerical proportion, defined by Faraday's law, exists between the quantity of electricity thus traversing the surface and the quantity of material chemically transformed. The degree of the interfacial potential-difference and the quantity of current passing the unit surface in unit time determine the nature and the rate of the chemical transformation.

Now there is no reason to limit phenomena of this kind to metallic surfaces. In consequence, however, of certain peculiarities of the metallic state, the potentials at metallic surfaces are usually much greater than at non-metallic surfaces, such (*e. g.*) as the surfaces of colloidal particles or living cells; moreover metals are the best conductors of electricity. Hence metals in contact with solutions can readily be made the source of electrical currents, and advantage is taken of this peculiarity in the construction of batteries. For example, in the Daniell cell, where zinc in dilute $ZnSO_4$ solution is connected with copper in concentrated $CuSO_4$ solution, the zinc surface readily gives off Zn^{++} ions which carry positive electricity to the adjoining solution, while the copper surface receives Cu^{++} ions which lose their positive charges and are deposited as metallic copper. And since under these conditions the tendency for zinc to ionize and pass into solution, and for copper to deionize and deposit as metal are both strong, a current with a considerable driving force or potential (*ca.* 1 volt) flows through the solution from zinc to copper when the circuit is closed. The Daniell cell is one typical example of the means by which chemical energy may be transformed into electrical energy through the intermediary of metallic conductors and solutions of electrolytes. The conditions under which this transformation takes place admit of infinite diversity in detail; but certain general features of constitution and arrangement are common to all such systems. There are always two reacting surfaces connected by conductors in such a manner that a circular flow of electricity is possible. At one surface (anode) positive electricity enters the solution from the metal; here the chemical changes in the solution are in general *oxidative* in character; at the other surface (cathode) the positive stream re-enters the metal and the chemical changes are of a *reducing* kind. Oxidations may themselves readily be made to produce electric currents; if two substances, one of which oxidizes (*i. e.,* is reduced by) the other, are dissolved in separate vessels con-

nected by a bridge of salt solution, and the two solutions are placed in metallic connection through platinum electrodes, the one substance oxidizes the other just as if the two were in contact. This is an example of what is known as "chemical distance-action," and depends, as in other cases of electrolysis, on the passage of electricity between solution and electrode; positive electricity passes from the one electrode (anode) to the oxidizable substance and to the other electrode (cathode) *from* the reducible (or oxidizing) substance. Conversely an external current conducted by platinum electrodes through a solution containing oxidizable and reducible substances will effect oxidations at the anode and reductions at the cathode. Oxidation thus implies *gain,* and reduction *loss* of positive charges by the substances undergoing chemical change; and this general fact is one of the clearest indications of the intimate dependence of chemical upon electrical change. Intermolecular transfers of electricity (*i. e.,* of electrons) apparently take place in all chemical reactions; but it is only when the materials are so arranged as to permit of the formation of electrical circuits, in which the specifically electrical phenomena can be isolated and observed separately, that direct evidence of this transfer is seen.

These brief references to the fundamentals of electrochemistry seem necessary in order to make clear some of the conditions of chemical change under the influence of surfaces other than metallic, especially the surfaces of living cells. It is first to be noted that electrical circuits may readily arise between different portions of a *continuous* metallic surface immersed in a solution; *i. e.,* it is not necessary that the two regions acting as electrodes should be separate pieces of metal connected by a wire which passes outside the solution. Such circuits are known as "local circuits," and the processes of chemical change or electrolysis associated with them are often spoken of as "local action." The rusting of iron in an aqueous solution is an example of such local action. Similarly local circuits may arise between different parts of a living cell or nerve fiber; thus an active region is always negative (in the galvanometric sense) to an adjoining resting region. The presence of local areas of different potential at the surface of a piece of iron in contact with an electrolyte solution can readily be detected by both chemical and electrical means. At the anodal regions, where the iron cations enter solution, they may combine with whatever anions are present, *e. g.,* in ordinary water they interact with carbonate or hydroxyl ions to form rust, while the cathodal

areas remain bright.   A rust spot once formed tends to *spread,*
because it forms itself a local cathode and hence induces reac-
tion in the adjoining unrusted region which acts as the anode
of the local couple.   And similarly we may infer that at the
surface of the living cell a local surface-oxidation, involving
entrance of positive charges into the cell from the solution, may
take place if simultaneously at another area of the cell-surface
positive electricity is free to leave the cell or negative to enter.
A local electrical circuit or bioelectric circuit would thus be
formed; such circuits, as well known, are associated with all
forms of physiological activity.   The chemical and other effects
of the local bioelectric circuit also tend to spread or to be trans-
mitted to adjoining regions, as we have seen.[14]

The normal bioelectric circuits must be regarded from the
same general point of view as the local circuits at metallic
surfaces.   They are apparently the expression of local chemical
action which is associated with the passage of electricity be-
tween the cell-surface and the adjoining solution.   Perhaps the
simplest way of conceiving the situation is to regard the proto-
plasm as forming one, and the medium (lymph or physiological
salt-solution) the other, of two adjoining phases; each of these
is a good conductor of electricity and can furnish ions to the
other phase.   The general resemblance to the case of a metal
in contact with an electrolyte solution is evident.   Whenever
the protoplasmic surface-layer exhibits at two different areas
unequal tendencies to combine chemically with substances
present in the adjoining medium or in the internal protoplasm,
or unequal power of transmitting or combining with ions
present in either protoplasm or medium, the conditions for an
electric circuit are present.   In other words, if the protoplasmic
surface-film and its adjoining medium are *homogeneous* chemi-
cally and physically there will be no potential-differences be-
tween different areas and no bioelectric circuits, just as a homo-
genous metallic surface in a homogeneous solution exhibits no
local circuits.   But, if the protoplasmic surface is locally altered,
e. g., by a mechanical impact or some local chemical action, a
local electrical circuit is formed; and the associated electro-
chemical effects of this circuit may be the direct or indirect
means of profoundly altering the whole cell-activity.   This,
expressed in a very general way, appears to be the essential
condition of the characteristic " irritability " of living proto-
plasm.   The composition and hence the electromotor proper-

[14] In two recent papers in *Amer. Journ. Physiol.,* 1915, Vol. 37, p. 348,
and 1916, Vol. 41, p. 126, I have discussed this parallel in greater detail.

ties of the protoplasmic surface-films are altered with a readiness which in many cases is extreme; the local electrical effects thus resulting induce chemical effects, by a process essentially identical with electrolysis, these effects are transmitted as already described, and a widespread disturbance of equilibrium may result, followed by some characteristic alteration of cell-activity. The sensitivity of protoplasm to outside influences appears to depend mainly upon the delicate and complex conditions of equilibrium, chemical and physical (including colloidal), existing in the complexly organized surface-film; for this reason the local composition and physical properties (*e. g.,* permeability) of the cell-surface are very readily altered, and local circuits arise. Here again there is a striking parallel with the conditions in metals; local circuits may be formed at many metallic surfaces under conditions similar to those causing stimulation in living cells; mechanical action (scratching, pressure, bending), light (photoelectric effects), change of temperature (thermoelectric effects), as well as direct chemical alteration or local changes in the concentration of the solution in contact with the metal (concentration-cell effects[15]), may all produce local circuits with associated chemical changes.

According to the foregoing theory of protoplasmic transmission, the current of the local bioelectric circuit which arises between the active and the adjacent inactive regions of the irritable element as the result of some local stimulus, affects the latter region in such a manner as to render it also active. A similar circuit then arises between this new region of activity and the inactive region beyond, and the latter is activated in its turn, and by a repetition of this process the state of activity is transmitted over the whole surface of the cell. It is evident that the current of any bioelectric circuit is partly intracellular and partly extracellular. The present theory implies that this current (positive stream) where it leaves the cell-surface to enter the medium, induces in the protoplasmic surface-film, by a process of which the first step is an electrolysis, a change of structure or composition which alters in a definite and constant manner the electromotor properties of that region of the surface, and hence gives rise to a new local circuit between it and the unaltered region beyond. The direction of the bioelectric current resulting from stimulation shows that the cell-surface during activity has characteristic electromotor proper-

[15] Osmotic stimulation in living cells may be directly due in many cases to such " concentration-cell " effects, rather than to the abstraction of water; in general the latent period of stimulation seems too short for the latter type of effect.

ties which are different from those which it has during rest;
it is more *negative* (in the galvanometric sense), *i. e.*, the posi-
tive stream enters the cell at the active region; and this nega-
tive condition is induced locally, along with excitation, wher-
ever a sufficiently intense current passes from the cell-surface
to the outside. It has long been known that the electric current
causes stimulation where it *leaves* the cell-surface, *i. e.*, at the
cathode of a pair of stimulating electrodes. It is a matter of
indifference, so far as the physiological effect produced is con-
cerned, whether the stimulating current is derived from an out-
side source or is generated by processes within the cell itself.
In the latter case, which is the case of normal transmission,
the active and the inactive regions of the cell-surface represent,
respectively, the two electrode areas (analogous to the local
anode and cathode of the local metallic circuit) of the bio-
electric circuit. The fact that stimulation is characteristically
a polar process is thus explained; chemical processes of oppo-
site nature take place where the current *enters* and where it
leaves the cell surface. We should expect, therefore, that if we
could obtain metallic surfaces covered by a thin surface-film,
e. g., of oxide, which is readily removed or altered by the
processes of electrolysis associated with local circuits, such
surfaces would exhibit chemical transmission-phenomena of a
kind essentially similar to those observed in living cells.

Phenomena of this kind have in fact long been known,
although their fundamental resemblance to the phenomena of
protoplasmic transmission has only recently been recognized.
For example, in the well-known rhythmical catalytic decom-
position of hydrogen peroxide in contact with mercury, the
rhythm of chemical activity is directly dependent upon the
alternate formation and dissolution of a surface-film of oxida-
tion-product ("peroxidate") which is formed by the inter-
action of the peroxide with the metal. This film is readily re-
duced electrolytically to metallic mercury at the cathode of the
local circuit which is formed wherever the film is broken
through so as to expose the unaltered mercury beneath; in this
local electrolysis oxygen is liberated and the free mercury sur-
face is reformed. When carefully purified mercury is used,
and the concentration and reaction (H-ion conc.) of the per-
oxide solution are properly adjusted, the film becomes very
sensitive to the action of such local circuits; a local rupture then
initiates a reaction which is rapidly transmitted over the whole
surface, causing progressive dissolution of the whole film. The
latter is then reformed and the process is repeated in regular

rhythm. Bredig and Antropoff have shown that the decomposition is most active near the boundary between the free and the film-covered mercury surface, *i. e.,* where the local current is most intense, and that the dissolution of the film takes place at the local cathode.[16] When the film reforms, the change of surface-tension, due to the altered electrical polarization, alters the shape of the surface and causes automatically a local rupture; a local circuit is thus formed and the reaction is again initiated and spreads because of the electrolytic effects at the margin, as just described. The wave of decomposition passing over the surface is associated with a variation of potential which may be registered with a string galvanometer; records thus obtained suggest electrocardiograms in the regularity of the rhythm and other features; the rate of this rhythm, like that of the physiological rhythms, may be modified by changes in the temperature or in the composition (*e. g.,* H-ion) of the solution. The potential-difference between the free and the film-covered portions of the surface is *ca.* 0.12 volt, the latter region being cathodal.

The whole process exhibits many striking biological analogies, which undoubtedly depend upon a close similarity in the fundamental physico-chemical conditions under which the chemical reactions take place in living systems and in non-living systems of this type. Reactions taking place at metallic surfaces appear to have a general tendency to fluctuations of tempo, often rhythmical in character; this is observed (*e. g.*) in the solution of many metals in nitric acid, and seems to be due essentially to the alternating formation and dissolution of resistant or polarizing surface-films of oxide or other material. Transmission-processes of the kind just described, associated with local electrical circuits and electrolysis, invariably form part of these phenomena. An especially striking instance of such transmission may readily be demonstrated in iron wires which have been exposed to strong nitric acid or other suitable oxidizing agent, so as to bring the metal into the peculiar temporarily non-reactive state known as *passivity.* When such a passive wire is placed in dilute nitric acid it remains unaltered as long as it is undisturbed; but if it be touched with a piece of normal or "active" iron a wave of chemical activity instantly sweeps over the whole wire, active effervescence and solution begin, and—if the acid is not strong enough to re-

[16] Cf. Bredig and Weinmayr, *Zeitschr. Physik. Chemie,* 1903, Vol. 42, p. 601; Antropoff, *ibid.,* 1908, Vol. 62, p. 513; Bredig and Wilke, *Biochem. Zeitschr.,* 1908, Vol. 11, p. 67.

passivate the metal—the reaction continues until the whole wire is dissolved. This " activation " of passive iron resembles the stimulation of living irritable cells in a number of essential respects ;[17] it can be induced *mechanically, e. g.,* by bending or scratching the wire, or *chemically, e. g.,* by reducing substances, or *electrically, e. g.,* by making the wire, while immersed in the acid, the cathode in an electrical circuit of sufficient intensity. This last experiment is especially interesting since it shows clearly the polar character of the electrical activation-process. In order to activate passive iron electrically the metal must be made the *cathode;* if it is made the anode, not only is there no sign of activation, but the wire is rendered more than normally resistant to other forms of activation, *e. g.,* mechanical. In other words, the anodal influence is of a *passivating* instead of an activating nature, and in fact an active wire may readily be passivated by making it the anode in a circuit of sufficient intensity. The whole behavior of the metal reminds one irresistibly of the behavior of irritable tissues like nerve, which are stimulated and rendered more irritable at the cathode of a current led into the tissue from a battery, and inhibited and rendered less irritable at the anode (electrotonus).

In the case of the wire the explanation is essentially simple. When the wire is made cathode the protective surface-film of oxide, to which the passive condition is due, is altered or removed by electrolytic reduction, and the metal is then free to dissolve in the acid; while when the wire is made anode, surface-oxidation and the formation of the passivating surface-film are promoted. The other activating agents also produce their effects by electrical means. A mechanical influence like scratching breaks the film and exposes the normal or active iron beneath, thus forming a local circuit in which the exposed or active area is the anode and the adjoining or film-covered area the cathode. The latter region is at once electrically activated, *i. e.,* it becomes anodal in its turn, and by the automatic repetition of the same process at further regions the state of activity is propagated over the whole surface. Similarly a reducing substance activates by locally removing the oxide coating, thus forming a local circuit. Contact of active iron or a base metal like zinc activates for a similar reason, by the formation of a local circuit at the region of contact, in which the passive iron is cathode. Contact of a nobler metal like platinum not only

[17] For a more complete description and discussion of this parallel, cf. my recent article, " Transmission of Activation in Passive Metals as a Model of the Protoplasmic or Nervous Type of Transmission," *Science,* N.S., Vol. 48, p. 51.

fails to activate passive iron, but it prevents or inhibits activation in the neighborhood of the contact, and in fact will induce passivation in an active wire; the reason for this difference of effect is that the noble metal forms the cathode when in contact with either active or passive iron; the latter, being then anodal, is subjected to a passivating instead of an activating influence. Platinum will in fact readily passivate active iron by simple contact. If a piece of platinum is pressed tightly against an iron wire which is undergoing active effervescence and solution in dilute nitric acid, within a few seconds the reaction is seen gradually to subside, at first near the region of contact and then farther away, until by degrees the whole wire becomes inactive. On examination it is then found to be passive. This is a case of the transmission of a passivating instead of an activating influence, and as such has also interesting biological analogies.

Both passivation and activation in metals are thus dependent on *electrical* influences, which tend automatically to be transmitted from place to place over the surface because of the electrochemical effects at the boundary between the active and passive areas. Without this transmission, activation of the passive wire as a whole by local contact or mechanical change would be impossible, just as stimulation of the whole cell or nerve fiber without transmission of the excitation-state would be impossible. The lack of graded response in certain cellular elements like heart-muscle cells or nerve fibers, which exhibit the so-called "all-or-none" type of behavior, depends upon this propensity of the local disturbance to be propagated and to involve the whole cell; and it is interesting to note that the same peculiarity is exhibited by passive iron wires in nitric acid. Either the wire is not activated at all by a mechanical shock or a brief touch with another metal, or it is activated *completely*. Once the local reaction is started it tends inevitably to spread over the whole surface. The rapidity of this spread in an iron wire immersed in nitric acid may be very great; the main reason for this high speed is the low electrical resistance of the local circuit under such conditions, combined with the existence of a very considerable potential difference between active and passive iron, equal to *ca.* 0.7 volt; hence the local current is intense and rapidly removes the protective surface-film, so that under favorable conditions the transmission takes place at a velocity of several hundred centimeters per second. This speed is comparable with that of the most rapid forms of protoplasmic transmission.

Another feature in which the propagation of the active state

in passive iron resembles protoplasmic transmission is the auto-matically self-limiting character exhibited by the local reaction under certain conditions. When a nerve is stimulated locally, that region responds and transmits its state of activity to the adjoining region, and then immediately returns to the resting state. In other words, the local change of state is temporary and is rapidly reversed; this explains why a *wave* of activity appears to pass over the tissue. In a normal nerve the local variation of electrical potential—the index of the local dis-turbance accompanying the passage of the impulse—rises rapidly to a maximum and then immediately subsides; in the frog's sciatic this curve of electrical variation is nearly sym-metrical and lasts *ca.* .002 second, an interval representing the total time occupied by the stimulation-process at any one region. Since the tissue at once returns automatically to rest when stimulation ceases, repeated stimulation is required to main-tain its activity. Apparently the local process *itself* originates conditions which check or inhibit activity in the same region, *i. e.*, the activity is *self-limiting* as well as self-propagating. This appears to be the essential reason why nervous and other protoplasmic activities are typically not continuous, but rhyth-mical or alternating in their character; something analogous to a "cut-off" mechanism seems inherent in the local stimula-tion-process. Now the case of passive iron is especially inter-esting and instructive because under certain conditions it exhibits just this type of automatically self-limiting local reac-tion. In sufficiently strong nitric acid (of s. g. 1.25 or higher) the passive wire, when activated by any means, exhibits a tem-porary wave of activity which is rapidly transmitted over the whole wire; the local reaction ceases spontaneously, after an interval varying from a few seconds to a small fraction of a second (becoming rapidly briefer as the strength of the acid increases), and the metal becomes again permanently passive; after an interval it may be again activated and the same process is repeated. A further interesting resemblance to the condi-tions in irritable tissues is that after the metal has returned to the passive condition, a certain time always elapses before it can be again completely reactivated; immediately after the re-action has ceased the iron wire gives only a slight and local response to the contact of an activating metal like zinc; in other words, the iron is temporarily *refractory* to activation; but within a short time and by progressive degrees it recovers its former sensitivity and transmits activation as before. As is well known to physiologists, irritable living tissues like nerve and muscle exhibit a similar insensitive or so-called "refrac-

tory" period immediately after stimulation; this refractory
state varies in its duration and degree in different tissues, being
brief in nerve and voluntary muscle and relatively prolonged in
"slow" tissues like heart muscle. Recovery of the sensitive
condition after activation thus requires time, in both the metal
and the living tissues; apparently in both cases some process
of reconstitution takes place in the surface-layer during the
interval.

In passive iron the spontaneous repassivation in strong acid
depends largely upon electrical conditions of the same kind as
those determining the transmission of activity; in brief, the
self-limiting and passivating effect is also due to the current
of the local circuit formed at the active-passive boundary, but
takes place at the *anode* of this circuit, while the activation
which determines transmission takes place at the cathode, as
we have seen. In the local circuit arising at the boundary
between the passive and active areas of the wire the passive
region is cathodal, the active region anodal. Now, just as the
activating influence at the cathodal region determines the trans-
mission of activity to that region, so the passivating influence
at the local anode tends to bring the reaction in this region to a
rest and induce passivity. A curious situation thus arises
wherever the activation-wave passes. The very process of ac-
tivation itself, by rendering the newly active region anodal,
brings into existence conditions which arrest the local activity
and cause repassivation. This explains why there is only a
temporary local reaction in acid of sufficient strength; the in-
fluence of the local current, added to that of the acid itself,[18]
immediately repassivates the active region. Hence the local
reaction is at once self-propagating and self-limiting, and ac-
tivation travels as a wave along the wire, the local process being
temporary and quickly reversed.

With regard to the refractory period immediately following
repassivation, only a hypothetical explanation is possible at
present, but it may be assumed that the newly formed passivat-
ing surface-film has not the consistency, thickness or other
properties necessary for its rapid and complete alteration or
removal by the local electrolysis; a certain time is therefore
required for the recovery of the peculiar equilibrium on whic.a
this sensitive condition depends. Analogous considerations

[18] In weak nitric acid (s.g. 1.20 or less) there is no spontaneous
passivation; the concentration of the acid must exceed a certain minimum
for this to take place. But if any local region is rendered more than
normally anodal by the adjacent contact of a noble metal, *e.g.* platinum,
passivation will take place even in the weak acid and will spread to other
regions of the iron wire, as already described.

apply in the case of an irritable tissue; the protoplasmic sur-
face-film must be reconstructed in order to reacquire its former
properties.

If, as we assume, the activation-process in the inorganic
model is similar in its general determining features to the
stimulation-process in the living tissue, we must conclude that
in a nerve or similar conducting element the current of the
local active-inactive circuit, at the same time as it activates
the adjoining resting region, also cuts short activity at the
active region itself and causes there a return to the resting
state. We have seen that activation in metals depends upon
the alteration of a continuous surface-film of peculiar composi-
tion (an oxide or oxidation-product not yet clearly defined),
which, when present, prevents the interaction between the
solution and the metal; its removal, which is readily effected
by electrolysis at the local circuit formed wherever the con-
tinuity of the film is interrupted, enables interaction to take
place. Now in living irritable tissues there is also definite
evidence that stimulation is associated with a temporary altera-
tion, structural and chemical, of the protoplasmic surface-film
or "plasma-membrane," involving an increase of permeability.
In the normal resting condition of the cell this membrane is
semi-permeable, *i. e.*, the cell-surface behaves as if impermeable
to diffusing water-soluble substances like sugar and neutral
salts although permeable to water; during stimulation there is
evidence that this semipermeability disappears temporarily,
and that such substances then enter and leave the cell with
greater readiness. The change in the electromotor properties
of the cell-surface (negative variation) during stimulation is
similar in direction and degree to that accompanying any
marked increase in permeability, such as that resulting from
injury, death, or the action of a cytolytic substance.[19] A local
increase of permeability will therefore give rise to a local cir-
cuit whose current, if sufficiently intense, will cause stimula-
tion, just as the local interruption of the passivating surface-
film in iron causes activation. If this is a true conception of
the stimulation-process in living tissues, it follows that the
current of the local bioelectric circuit must affect the proper-
ties of the protoplasmic surface-film in a definite and constant
manner through some process of local electrolysis. Where the
current stimulates, *i. e.*, where the positive stream leaves the
cell-surface, it induces increase of permeability; where it

[19] Cf. *Amer. Jour. Physiol.*, 1915, Vol. 37, pp. 357 seq., for a fuller
reference to these phenomena, and a comparison with "local circuit"
effects in metals; also *ibid.*, 1916, Vol. 41, p. 126.

arrests activity—*i. e.*, where it re-enters the surface from the medium—it restores (or is an essential factor in restoring) the resting condition of semi-permeability. It would thus appear that in typical protoplasmic transmission, as in nerve, processes of opposite kind take place in front of and behind the activation wave as it advances; beyond the wave-front, where the local current passes from cell to medium (see Fig. 1), the effect of the current is to increase the permeability (by inducing some unknown chemical or metabolic change in the surface-film); while behind the wave-front, where the current passes from medium to cell, it restores the altered surface-film to the original or "resting" condition. We see here again the characteristic physiological *polar* action of the electric current. At the two regions of the cell-surface, corresponding respectively to the anodal and cathodal regions of the metallic model, processes of chemically opposite kind are induced; hence the dependent physiological effects at the two regions are also opposite. Apparently the restoration of the surface-film is rapid in some tissues (*e. g.*, nerve) and gradual in others (*e. g.*, heart muscle); to this difference corresponds the difference in the duration of the refractory period. It is also interesting to note that the process of recovery or reconstitution takes place where the positive stream *enters* the cell-surface from outside; from general electrochemical analogies we should infer that oxidation-processes take place here, probably connected with synthesis. In general, oxidations appear to be essential to the processes of recovery in protoplasm,—*e. g.*, from fatigue, anesthesia or injury.

If we assume that the physico-chemical conditions at the cell-surface are similar, in the general manner indicated above, to those at metallic surfaces, the sensitivity, *i. e.*, chemical reactivity, of living protoplasm and its power of transmitting physiological influence lose much of their mysterious character and become in a measure intelligible. Oxidation at one region of the cell-surface, simultaneously with reduction at another region—as in the various oxidation-reduction elements of electrochemistry—may well be the condition of many metabolic processes. It should be noted that any such local surface-oxidation, implying entrance of the positive stream into the cell at that region, need not necessarily be associated with permanent chemical change (*e. g.*, reduction) at another region, since at the latter region the surface-film may conceivably act as a non-polarizable partition, giving off ions on the one face and receiving them on the other (like, *e. g.*, a zinc plate partitioning a $ZnSO_4$ solution interposed in a circuit). The cell-

surface appears to act as a reversible electrode relatively to cations, as Macdonald's work, together with that of Loeb and Beutner, clearly indicates,[20] and this peculiarity may be an important factor in permitting the ready formation of bioelectric circuits wherever the cell-surface is locally altered.

The existence of electrical currents between regions of unequal physiological activity in living tissues has been known since the time of Volta and Galvani, and varied and extensive observational data exist in this field. It seems that we are now also in a position to construct a consistent general theory of these phenomena. The bioelectric currents are the expression of local inequalities of electrical potential, which are themselves dependent upon local inequalities of chemical action at different regions of the cell-surface; these currents are therefore an index of chemical change in the protoplasm, *i. e.*, of metabolism,—especially of surface-metabolism. Conceivably almost any kind of chemical or physical alteration of the surface-film may alter its electromotor properties and give rise to local circuits. These circuits having once arisen, secondarily affect chemical processes at other regions traversed by the current-lines; this will take place wherever the local intensity and current-density are sufficient. Similarly, the passage of an electric current from outside through the living tissue or cell will produce changes of the same kind in the living substance. It is well known that entirely normal physiological effects may result from artificial electrical stimulation; the reason for this appears to be simply that the passage of electric currents across the cell-surfaces is a normal and constant condition of vital processes in general. In other words, electrical stimulation is a physiologically normal process, hence the physiological effects produced by artificial electric currents are normal. Such currents are produced in the normal activity of the cell, and once having arisen, they themselves furnish the necessary conditions for other physiological activities. This is particularly true of the phenomena of transmission, the special process under consideration in this article.

We have seen that chemical " distance-action " is characteristic of chemical reactions taking place in solutions in contact with metallic surfaces. Distance-action is also characteristic of the chemical processes in living organisms. Oxidation at one area of a platinum surface immersed in an electrolyte solution will induce reductions at other areas if reducible sub-

[20] J. S. Macdonald, *Proc. Roy. Soc.*, 1900, Vol. 67, p. 310; Loeb and Beutner, *Biochem. Zeitschr.*, 1912, Vol. 41, p. 1, and later papers in the same journal.

stances are there present.   The transmission of this influence
is instantaneous, since it depends upon the production of elec-
trical circuits associated with chemical change (electrolysis)
at the regions where electricity passes between the metal and
the solution.   In the case of surfaces like those of living cells
or nerve fibers, which resemble metallic surfaces in their funda-
mental electromotor properties, we may assume that similar
condition exist, differing in degree but not in kind.   This is
the general type of process under which we have included
above, as special cases of a peculiar kind, the various forms of
protoplasmic transmission.   The propagation of physiological
influence appears in fact inevitable wherever the cell is sensi-
tive to electrical stimulation; and the degree and rate of this
transmission are limited only by the electrical sensitivity of the
cell and the rate at which the bioelectric change develops.   In
the case of metallic surfaces it may readily be shown by a very
simple experiment that the electrical circuits produced by local
action will influence chemical processes at adjoining regions of
the surface up to a distance of several centimeters beyond the
region immediately affected.[21]   A piece of iron wire placed in
a solution of potassium ferricyanide (2–4 per cent.) in dilute
gelatine-solution or egg-white (which favors structure-forma-
tion by acting as protective colloid) will quickly form slender
blue filaments of ferrous ferricyanide at all points of the sur-
face.   If now another similar piece of wire, attached at one
end to a small piece of zinc or other base metal, be placed in the
same solution, the formation of filaments is found to be sup-
pressed or retarded for a distance of five to ten centimeters
(the effect decreasing with the distance) from the region of
contact.   In the local couple which is formed the zinc is anode
and the iron cathode; the liberation of ions from the iron is
thus hindered and the reaction prevented.   Or, conversely, the
contact of copper or platinum will hasten the formation of fila-
ments for a similar distance from the region of contact.   Simi-
lar experiments may be performed with other metals (zinc,
cadmium, cobalt, nickel) which form insoluble ferricyanides.
An experiment of this kind may be regarded as a simplified
model illustrating in an elementary manner the means by which
physiological influence may be transmitted from region to
region of the cell-surface.   As already pointed out, it is essen-
tial to the present theory of protoplasmic transmission that the
local excitation-process in (*e. g.*) a frog's motor nerve should
instantly induce excitation of the adjoining resting regions to

[21] Cf. *Biological Bulletin*, 1917, Vol. 33, p. 135, for a full account of
these phenomena, with a discussion of their biological parallels.

a distance of about three centimeters from the active region. The potentials are smaller and the resistances greater in the bioelectric circuits than in those formed in the above metallic models, but in other respects the conditions are closely comparable.

In conclusion it may be again pointed out that the curious reciprocality of many physiological processes—a peculiarity probably connected with the tendency to rhythmical or alternating activity so frequent in organisms—in itself suggests a general explanation of this kind. Processes of growth, excitation, or metabolic activity at one region are often associated with prevention or inhibition of these processes at adjoining regions; the central nervous system is not the only living structure exhibiting this phenomenon of "reciprocal inhibition," although it is clearest here.[22] We must note the fact, which I believe is more than a coincidence, that a similar chemical reciprocality obtains between the two electrode areas of any electrical circuit dependent on chemical action. Oxidation at the one area involves reduction at the other area; similarly in living organisms, excitation at one region conditions the inverse process of inhibition at another region. Obviously these physiological processes have their underlying and determining chemical reactions. If these are in large part electrically controlled, the physiological reciprocality becomes at once intelligible; the essential chemical or metabolic processes are oppositely affected at the two regions corresponding to the electrode areas of the circuit. Activities controlled by such means may *alternate* but cannot take place simultaneously. Where we find, as we do in organisms, this reciprocality of control associated with the transmission of physiological or chemical influence to a distance, it is natural to ask the question if the essential determining conditions of the vital process are not of the same fundamental nature as those of the non-vital process which shows similar general peculiarities. Apparently in the transmission of excitation from region to region in an irritable cell or nerve fiber we have merely one instance of the control of physiological processes by means of the bioelectric currents produced in activity. The characteristic electrical sensitivity of living matter seems in itself to be an indication that the chief normal or physiological means of controlling and correlating cell-processes are electrical. A fundamental problem of general physiology is therefore to determine more definitely the physico-chemical basis of this electrical sensitivity.

[22] The phenomena of simultaneous contrast in vision form apparently another example of this influence. The processes in adjoining retinal areas affect one another reciprocally and the effect is greatest near the boundary of the two areas.